DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 7/30/2009, are acknowledged and entered. Claims 8, 13, 17, and 21 have been cancelled by Applicant. Claim 28 is newly added. Claims 1-4, 7, 11-12, 16, 20, and 28 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claims 8, 13, 17, and 21 are withdrawn as being moot in light of Applicant's cancellation of the claims.

Applicants' arguments, filed 7/30/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Upon further consideration, a new ground of rejection under 35 U.S.C. 112, 1st Paragraph is being made with regard to the limitation "a potentiating ratio". Because this rejection could have been made in a previous Office Action, this Office Action is **Non-Final**.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statements filed 4/29/2009, 5/20/2009, and 10/1/2009. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Declaration under Rule 1.132

The Examiner acknowledges receipt of the Rule 1.132 Declaration of Hakim Djeha ("Djeha" Declaration) and has carefully considered the information provided therein.

Claim Objections

Claim 28 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claim 28 depends from claim 1, which recites the treatment of "solid cancerous tumors". Claim 28 recites specific solid cancerous tumors in addition to reciting "leukemia". One skilled in the art would not recognize that leukemia is a "solid cancerous tumor" because leukemias are cancers of blood-cells and do not form solid tumors.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 7, 11-12, 16, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 2, it is unclear whether the potentiating ratio in a range of 1:100 to 1:2 refers to a ratio of DMXAA:gemcitabine or gemcitabine:DMXAA.

Regarding claim 7, the claim recites a pharmaceutical dosage comprising DMXAA or a salt thereof "in an amount to provide a dosage range of 500 to 4900 mg/m^2" and gemcitabine "in a potentiating ratio" in a mammal. The claim is unclear with regard to how much of each agent is present in the composition. The limitation "to provide a dosage range of 500 to 4900 mg/m^2" does not clearly define how much DMXAA is present in the dosage form. While it is acknowledged that Applicants state that a dose of 500 to 4900 mg/m^2 is suitable for administration to a subject with cancer in practicing the *methods* of the invention, there is no disclosure regarding how much DMXAA need be present in a *dosage form* to provide this dose range. For example, DMXAA in an amount of 100,000 mg could provide a dosage of 500 to 4900 mg/m^2 depending on at what rate the DMXAA is administered and for how long it is

administered. Similarly, DMXAA in an amount of 0.001 mg could provide a dosage of 500 to 4900 mg/m^2 if it is administered over a long period of time.

Regarding claims 7, 11-12, 16, and 20, the limitation "a potentiating ratio" does not define the amounts of DMXAA and gemcitabine present in the claimed formulations and kits. A "potentiating ratio" relates to potentiation of anticancer activity and thus to doses administered to subjects. However, the instant claims are pharmaceutical formulation and kits, not methods of treatment. As such, defining the amounts of DMXAA and gemcitabine as being present in "a potentiating ratio" does not clearly and distinctly claim the amounts of these agents intended to be present in the claimed pharmaceutical formulations. For example, while Applicants disclose that a "potentiating ratio" is a ratio in the range of 1:100 to 1:2 (claim 2), is it Applicant's intent that a composition comprising 0.001 mg DMXAA and 0.002 mg gemcitabine is a "potentiating ratio" as recited in the instant claims? It is unlikely that such low doses would have any therapeutic effect at all, let alone a synergistic effect. Is it Applicant's intent that 100,000 mg DMXAA and 10,000,000 mg gemcitabine (a ratio of 1:100) present in a pharmaceutical formulation is a "potentiating ratio"? Furthermore, it is unclear for what the ratio is "potentiating".

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7, 11-12, 16, 20, and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination

of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims recite "a potentiating ratio" of DMXAA and gemcitabine. The specification discloses that the term "potentiating ratio" is used to indicate that the DMXAA or pharmaceutically acceptable salt thereof and the other compound are present in a ratio such that the antitumor activity of the combination is greater than that of DMXAA alone or the compound alone or of the additive activity that would be predicted for the combinations based on the activities of the individual components in a test (page 3, lines 13-25). For DMXAA and antimetabolites such as gemcitabine, a potentiating ratio is disclosed to be in the range of 1:100 to 1:2 DMXAA:antimetabolite (page 4, lines 17-24).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117).

In the instant case, there is only one example of DMXAA and gemcitabine being administered in a "potentiating ratio" (Example 2). In this example, DMXAA and gemcitabine were administered to pancreatic tumors in a ratio of 1:12 (DMXAA:gemcitabine). There are no other examples providing of "a potentiating ratio" of DMXAA and gemcitabine in the disclosure. In the example provided in the Declaration of Hakin Djeha, filed 3/23/2009, DMXAA and gemcitabine were administered to treat lung cancer tumors in a ratio of 1:13.3 (DMXAA:gemcitabine). However, in this example for the treatment of lung tumors, the ratio of 1:13.3 was not a "potentiating ratio" because the combined drug effect was not greater than that of DMXAA alone (see Figures 2 and 3).

It is further noted that the prior art does not provide a recognition of ratios of DMXAA to gemcitabine that are "potentiating ratios".

Accordingly, the claims and specification do not provide written support within the meaning of 35 U.S.C. 112, 1st Paragraph for the claimed "potentiating ratio". Only one such ratio is demonstrated by Applicants (1:12) and only for treating pancreatic tumors. The Declaration of Hakin Djeha, filed 3/23/2009, clearly demonstrates that a "potentiating ratio" (*e.g.*, ~1:12) in one tumor type is not necessarily a "potentiating ratio" in other tumor types.

Requiring the skilled artisan to carry out random, hit-or-miss testing in order to experimentally determine through extensive *in vivo* testing what doses of DMXAA and gemcitabine when administered in combination to treat tumors or are present in a pharmaceutical dosage or kit constitute a "potentiating ratio" is *prima facie* evidence that Applicants were not in possession of such ratios at the time the invention was made. Furthermore, as noted above, while a dose of 0.001 mg DMXAA and 0.002 mg gemcitabine clearly falls within the range suggested by Applicants (*i.e.*, a ratio of 1:2), one skilled in the art would not expect such doses, if administered to treat a tumor, would be therapeutically effective, let alone "potentiating". Note that the instant claims recite "an effective amount", not a *therapeutically* effective amount of DMXAA and gemcitabine. As such, doses of 0.001 mg DMXAA and 0.002 mg gemcitabine clearly fall within the scope of the claimed "effective amount".

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed "potentiating ratio". One of skill in the art would not recognize from the disclosure that the applicant was in possession of the claimed ratios purported to be "potentiating" in the treatment of tumors. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 1-3, 7, and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim 1 recites a method of treating a solid cancerous tumor comprising administering 500 to 4900 mg/m^2 DMXAA and gemcitabine "in a potentiating ratio". Claim 2 recites that the

potentiating ratio is in a range of 1:100 to 1:2. Claim 7 recites a pharmaceutical dosage comprising DMXAA in an amount to provide a dosage in a range of 500 to 4900 mg/m^2 and gemcitabine in a "potentiating ratio" in a mammal.

The combined limitations of a dose of 500 to 4900 mg/m^2 DMXAA with gemcitabine and "in a potentiating ratio" in the claims introduces new matter.

Applicants disclose that the dose of gemcitabine useful in the invention ranges from 400 to 2000 mg/m^2 (page 17, lines 6-9). Applicants further disclose that a "potentiating ratio" is in the range of 1:100 to 1:2 (DMXAA:gemcitabine) for DMXAA combined with an antimetabolite such as gemcitabine (see claim 2 and page 4, lines 17-20). The claims thus encompass administering 1000 mg/m^2 (1:2) to 50,000 mg/m^2 (1:100) gemcitabine when DMXAA is 500 mg/m^2 or 9800 mg/m^2 (1:2) to 490,000 mg/m^2 (1:100) gemcitabine when DMXAA is 4900 mg/m^2. Alternatively, the claims encompass administering 4 mg/m^2 DMXAA (1:100) to 200 mg/m^2 DMXAA (1:2) when gemcitabine is administered in a dose of 400 mg/m^2 or 20 mg/m^2 DMXAA (1:100) to 1000 mg/m^2 DMXAA (1:2) when gemcitabine is administered in a dose of 2000 mg/m2.

Because the instant disclosure only provides written support for 400 to 2000 mg/m^2 gemcitabine or 500 to 4900 mg/m^2 DMXAA as discussed above, the dose ranges of gemcitabine and/or DMXAA now encompassed by the claims are not supported by the disclosure.

Claims 1-3 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pancreatic tumors comprising administering DMXAA and gemcitabine in a ratio of 1:12, does not reasonably provide enablement for the treatment of other solid cancerous tumors with DMXAA and gemcitabine in the claimed "potentiating ratio". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

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[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment of solid cancerous tumors comprising administering DMXAA in a range of 500 to 4900 mg/m2 and administering an effective amount of gemcitabine wherein DMXAA and gemcitabine are administered "in a potentiating ratio". The instant disclosure states that a "potentiating ratio" is used to indicate that the DMXAA or pharmaceutically acceptable salt thereof and the other compound are present in a ratio such that the antitumor activity of the combination is greater than that of DMXAA alone or the compound alone or of the additive activity that would be predicted for the combinations based on the activities of the individual components in a test (page 3, lines 13-25). For DMXAA and antimetabolites such as gemcitabine, a potentiating ratio is disclosed to be in the range of 1:100 to 1:2 DMXAA:antimetabolite (page 4, lines 17-24).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

The instant disclosure demonstrates that administration of 20 mg/kg DMXAA and 240 mg/kg gemcitabine (i.e., a ratio of 1:12) provides an enhanced effect relative to DMXAA alone

in treating pancreatic tumor volume tripling and doubling times (Example 2). Objective evidence submitted by Applicants (see Declaration of Hakim Djeha filed 3/23/2009) demonstrates that when administered in a similar ratio (i.e., 1:13.3), DMXAA (18 mg/kg) and gemcitabine (240 mg/kg) did not result in an enhanced effect relative to DMXAA alone when administered to treat lung tumors (see especially Figures 2 and 3). This evidence casts significant doubt on Applicant's assertion that administration of DMXAA and gemcitabine in combination to treat solid cancerous tumors can be administered in a "potentiating ratio" wherein the DMXAA or pharmaceutically acceptable salt thereof and the other compound are present in a ratio such that the antitumor activity of the combination is greater than that of DMXAA alone or the compound alone or of the additive activity that would be predicted for the combinations based on the activities of the individual components in a test (page 3, lines 13-25). It is evident from the example provided in the Declaration of Hakim Djeha that DMXAA and gemcitabine in a ratio of 1:13.3 was no more effective in inhibiting lung tumor growth than DMXAA alone.

2. The breadth of the claims

The claims are extremely broad insofar as they disclose the general treatment of solid cancerous tumors with DMXAA and gemcitabine wherein the DMXAA and gemcitabine are administered in a "potentiating ratio".

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides only general guidance and direction with regard to the claimed treatment methods. In this regard, Applicants define what is meant by a "potentiating ratio" (page 3, lines 13-25) and disclose that for DMXAA in combination with an antimetabolite such as gemcitabine, the ratio is 1:100 to 1:2 (page 4, lines 17-24). Applicants teach that the amount of DMXAA will be from 500 to 4900 mg/m2 (page 15, line 23 to page 16, line 9; claim 2) and the amount of gemcitabine will be from 400 to 2000 mg/m2 (page 17, lines 5-18). Applicants further disclose that a "potentiating ratio" is in the range of 1:100 to 1:2 (DMXAA:gemcitabine) for DMXAA combined with an antimetabolite such as gemcitabine (see claim 2 and page 4, lines 17-20). The claims thus encompass administering 1000 mg/m^2 (1:2) to 50,000 mg/m^2 (1:100)

gemcitabine when DMXAA is 500 mg/m^2 or 9800 mg/m^2 (1:2) to 490,000 mg/m^2 (1:100) gemcitabine when DMXAA is 4900 mg/m^2. Alternatively, the claims encompass administering 4 mg/m^2 DMXAA (1:100) to 200 mg/m^2 DMXAA (1:2) when gemcitabine is administered in a dose of 400 mg/m^2 or 20 mg/m^2 DMXAA (1:100) to 1000 mg/m^2 DMXAA (1:2) when gemcitabine is administered in a dose of 2000 mg/m2. No reasonably specific guidance is thus provided for the amounts of DMXAA and gemcitabine intended to be administered in Applicant's methods in potentiating ratios.

The instant specification provides a single working example wherein 20 mg/kg DMXAA and 240 mg/kg gemcitabine (*i.e.*, a ratio of 1:12) provides an enhanced effect relative to DMXAA alone in treating pancreatic tumor volume tripling and doubling times (Example 2). No other ratios of DMXAA to gemcitabine were tested and no examples are provided regarding the treatment of other solid tumors.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used in a "potentiating ratio" as a treatment for all solid cancerous tumor growths as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because DMXAA and gemcitabine administered in a ratio of 1:12 to pancreatic tumors results in an enhanced effect then any ratio from 1:100 to 1:2 of DMXAA to gemcitabine must, *a priori*, be a "potentiating ratio" useful in the treatment of any solid cancerous tumor growth, wherein the combined effect is greater than that of DMXAA alone or the compound alone or of the additive activity that would be predicted for the combinations based on the activities of the individual components in a test (page 3, lines 13-25). However, the claims encompass the treatment of a plethora of

biologically and histologically distinct tumors with a wide range of ratios and/or doses of DMXAA and gemcitabine. Applicants tested one such ratio of DMXAA and gemcitabine in one tumor type. Objective evidence suggests that this ratio does not result in an enhanced therapeutic effect in other tumor types (*e.g.*, lung tumors).

Determining if any particular claimed tumor type would be treated with any particular ratio of DMXAA to gemcitabine wherein the combined effect is "potentiating" would require subjecting the combination to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 4 is rejected under 35 U.S.C. § 103(a) as being unpatentable over **Davis *et al***. (WO 00/48591; Published August 24, 2000) in view of **Peters *et al***. (Pharmacology & Therapeutics, 2000, vol. 87, pages 227-253)

The instant claim is drawn to a method of treating a solid cancerous tumor comprising sequentially administering an effective amount of DMXAA and an effective amount of gemcitabine.

Davis teaches methods of inhibiting the formation of new vasculature by angiogenesis comprising administering a combination of a vasculature damaging agent and an inhibitor of the formation or action of nitric oxide in mammalian systems (Abstract).

With respect to DMXAA as recited in claim 4, Davis teaches that 5,6-dimethylxanthenone acetic acid (*i.e.*, DMXAA) is a chemical compound shown to have vascular damaging activity against the newly formed endothelium of solid tumors (page 1, lines 26-27) and is exemplified as an agent useful in the invention (page 3, line 31 ; page 4, line 31).

With respect to gemcitabine as recited in claim 4, Davis teaches that the vasculature damaging agent/nitric oxide inhibitor combinations disclosed therein can be administered in combination with other treatments, including antimetabolites such as 5-fluorouracil, cytosine arabinoside, and hydroxyurea (page 2, lines 27-32). For the treatment of solid tumors, the combination may be administered in combination with other anti-tumor agents (page 6, lines 20-23) and exemplifies antimetabolites (page 6, line 25) as one genus of anti-tumor agents.

With respect to sequentially administering DMXAA and gemcitabine as recited in instant claim 4, Davis teaches that combination therapy may involve simultaneous or sequential application of the individual components of the treatment, thus motivating sequential administration as instantly claimed (page 6, lines 30-32).

Davis differs from the instant claims in that, while Davis discloses combining a vasculature damaging agent and nitric oxide inhibitor with antimetabolite anti-tumor agents, Davis does not explicitly disclose the claimed antimetabolite, gemcitabine.

However, Peters *et al.* discuss the basis for combination cancer chemotherapy with antimetabolites. In this regard, Peters *et al.* teach that anticancer agents are rarely used singly to treat cancer because only a few tumors are sensitive enough to be cured by single agents. Rather, effective chemotherapy usually depends on the identification of suitable combinations to treat a specific type of tumor (page 228, left column, first paragraph). With respect to antimetabolites, Peters *et al.* teach that antimetabolites are widely used in cancer combination chemotherapy, either together with another antimetabolite or with another anticancer agent

(paragraph bridging pages 231 and 232). Peters *et al.* disclose that a promising new type of combination is that of an antimetabolite with inhibitors of angiogenesis (page 233, right column). Table 1 of Peters *et al.* (page 234) discloses examples of commonly used effective combinations of antimetabolites with other anticancer agents. Table 5 of Peters *et al.* (page 244) specifically discloses combinations of **gemcitabine** with other anticancer agents, including 5-fluorouracil, CDDP, carboplatin, docetaxel, ifosfamide, navelbine, paclitaxel, vinorelbine, etoposide, and doxorubicin. Such combinations have been found to be effective for treating pancreatic, head and neck, mesothelioma, ovarian, bladder, NSCLC, SCLC, and breast cancers.

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined DMXAA, a nitric oxide inhibitor, and gemcitabine for the treatment of solid tumors. The skilled artisan would have been motivated to do so because Davis suggests and motivates combining a vasculature damaging agent such as DMXAA with an inhibitor of nitric oxide synthesis for the treatment of solid tumors wherein such a combination can also be combined with an additional antitumor agent such as an antimetabolite agent. While Davis does not teach that gemcitabine as recited in the instant claims is such an antimetabolite agent, Peters *et al.* teach that antimetabolite agents such as gemcitabine are routinely combined with other chemotherapeutic agents and regimens for the treatment of cancer. As such, the skilled artisan would have been imbued with at least a reasonable expectation that a combination of DMXAA, an inhibitor of nitric oxide synthesis, and gemcitabine would be effective in the treatment of solid tumors as suggested and motivated by the cited prior art.

The Examiner would like to draw Applicant's attention to the following:

"[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". *KSR v. Teleflex*, 127 S,Ct. 1727, 1740 (2007) (quoting *Sakraida v. A.G. Pro*, 425 U.S. 273, 282 (1976). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (*id.*). Addressing the issue of obviousness, the Supreme Court noted that the analysis

under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007).

The Court emphasized that "[a] person of ordinary skill is... a person of ordinary creativity, not an automaton." *id* at 1742. Consistent with this reasoning, it would have been obvious to have selected various combinations of various disclosed ingredients from within a prior art disclosure, to arrive at compositions "yielding no more than one would expect from such an arrangement". In this instance since the prior art teaches potentiating effects of the combination of DMXAA with an inhibitor of nitric oxide synthesis wherein such a combination can be combined with other anticancer drugs, it would have been obvious to one of ordinary skill in the art to select gemcitabine as an antimetabolite agent suggested in Davis in combination with DMXAA and an inhibitor of nitric oxide synthesis and test this combination of drugs for antitumor activity.

Response to Arguments

Applicants traverse the instant rejection, stating that: 1) Davis teaches a "laundry list" of anticancer agents that may be used in combination with DMXAA and NO synthase inhibitor and does not disclose any potentiation of the vascular damaging agents and inhibitors of nitric oxide with any additional agents and more specifically, gemcitabine, let alone a potentiating ratio of DMXAA and gemcitabine and 2) there is no suggestion or motivation to "modify" Davis to arrive at the claimed invention.

Regarding 1) above, Davis explicitly suggests and motivates treating tumors with a vascular damaging agent and nitric oxide synthase inhibitor as a sole therapy or in combination with other treatments. One such other treatment is combination with other anti-tumor substances such as antimetabolites (page 2, lines 25-32). DMXAA is explicitly disclosed as a suitable vascular damaging agent (page 3, line 31; page 4, line 31). Doses of vascular damaging agent are disclosed to be in the range of 10-1000 mg/m^2 (page 6, lines 8-9). Peters et al. disclose what is well-known in the art: gemcitabine is an antimetabolite anticancer agent useful in the treatment

of various cancers alone and in combination with other therapeutic agents. As such, the skilled artisan would expect that DMXAA + nitric oxide synthase inhibitor + gemcitabine would be effective to treat tumors. The only "modification" of Davis required to arrive at Applicant's invention is selection of an antimetabolite agent not explicitly disclosed in Davis. However, such a selection is an obvious modification of Davis because the skilled artisan would recognize that the antimetabolite agents disclosed in Davis are merely examples, not an exhaustive list. Regarding "potentiation", the instant claim does not recite that DMXAA and gemcitabine are administered in a potentiating ratio, only that "an effective amount" is administered. Such effective amounts are disclosed in the cited prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614